PSYCHOMOTOR FUNCTIONING: COMPARISON OF PATIENTS RECOVERING FROM GENERAL ANESTHESIA WITH REMIFENTANIL AND A VOLATILE ANESTHETIC VERSUS FENTANYL AND A VOLATILE ANESTHETIC

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ABSTRACT

A new opioid, remifentanil, recently gained approval for clinical use by the Food and Drug

Administration. This has given anesthesia providers another agent with which to conduct

anesthesia for both inpatient and outpatient surgery. Remifentanil has markedly different

pharmacokinetics from other commonly used opioids. Specifically, remifentanil provides a

predictable and rapid termination of action -- a potential advantage over other opioids.

The purpose of this study was to compare how remifentanil and another more

commonly used opioid, fentanyl, affect one aspect of anesthesia recovery -- psychomotor

functioning. Twenty three subjects were sampled. Subjects received a balanced anesthetic

using either remifentanil and a volatile agent, or fentanyl and a volatile agent.

The Trieger Dot test was the assessment tool used to assess for baseline and recovery of

psychomotor functioning. A test-retest reliability coefficient of 0.76 was obtained.

Analysis of data did not reveal significant differences in psychomotor recovery

between the two groups. Possible reasons behind this may have been related to the study's

design. Due to the short duration of action associated with remifentanil, all subjects who

received remifentanil also received other intraoperative opioids. These may have

influenced postoperative psychomotor functioning postoperatively. Additionally, variety in

case procedure, length, and the amount of anesthesia required may have significantly

influenced postoperative psychomotor functioning.

KEY WORDS: remifentanil, fentanyl, postoperative psychomotor recovery, psychomotor
assessment, Trieger Dot test

PSYCHOMOTOR FUNCTIONING: COMPARISON OF PATIENTS

RECOVERING FROM GENERAL ANESTHESIA WITH

REMIFENTANIL AND A VOLATILE ANESTHETIC

VERSUS FENTANYL AND A VOLATILE

ANESTHETIC

by

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I: INTRODUCTION

Outpatient Surgery Expansion

Healthcare is in a of state flux with an increasing emphasis being placed on outpatient surgery as an alternative to traditional inpatient surgery. The American Hospital Association reported that in 1993, 55% of all surgeries at community hospitals were performed on an outpatient basis. That is remarkable considering that in 1983, only 24% of all surgeries were done on an outpatient basis (American Hospital Association, 1994). This increase in number of cases is matched by an expansion in types of cases considered to be appropriate for outpatient surgery. Today, outpatient surgeries run a broad spectrum from dental extractions and excision of skin lesions to more invasive surgeries such as laparoscopies and septorhinoplasties (White & Smith, 1994).

This growing acceptance of outpatient surgery can be shown by comparing American Society of Anesthesiologists (ASA) physical classifications of today's outpatient candidates as opposed to the classifications of outpatient candidates in years past (White & Smith, 1994). This classification system described by Dripps, Lamont, and Eckenhoff (1961) has been utilized by anesthesia providers since 1962 ("New Classification", 1963). Surgical candidates are classified by physical status on a scale of I through V. A score of I signified an assessment of good health with no apparent health risks contrasted to a score of V signifying an assessment of moribund health. At one time, only ASA physical classification I patients were considered as candidates for outpatient surgery. Today, patients classified as ASA II and III may be considered as candidates for outpatient surgery (White & Smith, 1994).

Many factors have contributed to this marked increase in the volume and variety of outpatient surgeries. A major impetus for this expansion has been the desire of third party payers to contain costs. Paul White (1996), Professor and McDermott Chair of Anesthesiology and Pain Management, the University of Texas Southwestern Medical Center, estimates that an outpatient procedure reduces costs by 25 to 75% when compared to the same procedure performed on an inpatient basis. Other factors have also made the choice of outpatient surgery appealing. For the institution, the availability of an inpatient bed is not requisite to accommodate the case. For the patient, there are benefits such as increased flexibility in scheduling the procedure, less time away from home, and decrease in iatrogenic infections. A common thread running through all benefits is reduced length of patient stay.

<div align="center">Factors Affecting Postoperative Stay</div>

The length of patient stay postoperatively is dependent upon many factors. Certain factors, such as intraoperative complications and the patient's background stress, are beyond the practitioner's locus of control (White & Smith, 1994; Liu, Barry, & Weinman, 1994). Other factors, however, can be manipulated by the anesthesia provider throughout the perioperative period to decrease the length of stay. Preoperative psychological preparation, pharmacologic anxiolysis, and adequate hydration with intravenous fluids have each been shown to facilitate postoperative recovery (Liu, *et al.*, 1994; Weldon, Watcha, & White, 1992; Yogendran, Asokumar, Cheng, & Chung, 1995). Intraoperatively, the choice and implementation of anesthetic techniques influences residual drug effect postoperatively (White & Shafer, 1988). Postoperatively, an expedited and satisfactory discharge is dependent upon acute awareness and intervention

by practitioners (Green & Jonsson, 1993). During this period, home readiness may be affected by any one of several persistent symptoms. Pain, nausea and vomiting, hypotension, and an unsteady gait are examples of such persistent symptoms (Chung, 1995).

Stages of Recovery

Ultimately, the length of stay postoperatively is a function of how rapidly the patient recovers from the surgery. Sujit and Uma Pandit (Pandit & Pandit 1997) describe recovery by classifying it into four distinct stages. Stage I of recovery, "Emergence", ends when the patient responds to verbal commands and frequently is attained while the patient is still in the operating room. Stage II, "Early Recovery", is completed when the patient is awake and alert, hemodynamically stable, can maintain his own airway, and has return of protective reflexes. This is usually attained within 15-60 minutes postoperatively. Stage III, "Home Readiness", is reached when the patient can walk without assistance and side effects such as orthostatic hypertension, drowsiness, and bleeding have subsided. Attainment of this stage is highly variable, ranging from 60 minutes to 6 hours. Stage III generally must be completed prior to discharge to home. Stage IV, "Street Fitness", is even more variable than stage III and is usually attained at home within days or weeks. This is the stage of recovery that must be attained before the patient drives an automobile or engages in other activities that would require a high level of cognitive functioning.

Psychomotor Functioning

Psychomotor functioning is integral to stage III of postoperative recovery, "Home Readiness". Within that context, it will be the focus of this study. The word "psychomotor" refers to physical activity associated with mental processes (Taber's, 1985).

Assessment of psychomotor functioning generally is measured with visual motor stimuli and/or reaction times (Cashman & Power, 1989; Newman, Trieger, & Miller, 1969). Paper and pencil tests such as the Trieger Dot test and digit symbol substitution test are easily administered and are inexpensive ways to assess psychomotor function (Newman, *et al.*, 1969; Beck, Feshbach, & Legg, 1962). Further, these tests require minimal effort from the patient. Researchers' concerns with these types of tests, however, are practice effects--improvement in score from baseline with repeated testing--and validity (Gottlieb, Corcos, Jaric, & Agarwal, 1988; Lichtor, 1997). Other tests which serve as artificial meters of psychomotor functioning require electronic equipment. These tests, such as the tapping board test and the Maddox wing test, are more accurate measurements of psychomotor functioning. However, administration of these tests may not be practical in every setting due to logistical requirements and expense (Lichtor, 1997).

<div align="center">Anesthetic Choice</div>

Intraoperative anesthesia is a factor that will impact the speed of a patient's postoperative recovery. Choice of an anesthetic to provide for minimal residual postoperative drug effect is, however, a secondary consideration. The choice of anesthetic for a case must be tailored to meet the needs of the patient, the surgeon, and, to a certain extent, the institution where the surgery is being performed. Foremost in the anesthetist's

mind are the patient's safety and the efficacy of the chosen anesthetic technique. Patient

related considerations such as age, pre-existing disease, substance abuse, obesity,

anesthetic history, and patient preferences are considered when determining the

appropriateness of an anesthetic technique (Feely & Botz, 1997; Turner, Scarpace, &

Lowenthal, 1992; Baker, 1994).

<div align="center">Balanced Anesthesia</div>

This study will utilize balanced anesthesia as the technique of choice when a

general anesthetic is desired. It was first described in 1926 by John S. Lundy (1942) as,

"the use of a combination of anesthetic agents and methods so balanced that part of the

burden of relief of pain is borne by preliminary medication, part by local anesthesia, and

part by one or more general anesthetic agents (p. 559)". Today, balanced anesthesia is the

most commonly chosen form of general anesthesia for outpatient surgery (Pandit &

Green, 1994).

General anesthesia connotes blockade of mental, sensory, reflex, and motor

functions (Woodbridge, 1957). Mental blockade refers to sedation, amnesia, and

unarousable deep sleep. Sensory blockade refers to minimizing systemic response to

noxious stimuli. Reflex blockade refers to control of unwanted cardiovascular,

respiratory, and gastrointestinal responses to surgery or anesthesia. Motor blockade refers

to interruption of the neuromuscular junction so as to relax striated muscle tone. There

are many classes of drugs used to achieve these various blockades. Intravenous

sedative/hypnotics such as propofol may be used for mental blockade (Smith, White,

Nathanson, & Gouldson, 1994). Inhalational anesthetics such as isoflurane may serve as

agents for both mental and sensory blockade. Opioids like fentanyl may also be relied

upon for sensory and/or mental blockade (Lemmens, 1995). Reflex blockade for

maintenance of internal homeostasis may be provided for by additional effects of the

above mentioned agents or by adjuvant drugs such as atropine (Katzung, 1995).

Curariform drugs like rocuronium may provide for motor blockade (Griffith & Johnson,

1942).

      This research will examine the impact of the choice of opioids on outpatient

surgery when employed in a balanced anesthetic. The focus will be on comparing the

effect that two opioids, fentanyl and remifentanil, have on psychomotor function

recovery postoperatively. Fentanyl, as opposed to newer phenylpiperidines, is being

compared to remifentanil in this study because of its long history of use in balanced

anesthesia as well as its continued ubiquitous usage. Both opioids are used for their

intraoperative central nervous effects of analgesia and sedation. Postoperatively,

however, impaired psychomotor functioning is a concern with opioids in outpatient

surgery (Pandit & Pandit, 1997).

      Fentanyl is a phenylpiperidine μ-selective (*mu*-selective) opioid (Feldman, *et al*.,

1991). Remifentanil is also a phenylpiperidine μ-selective opioid (Amin, *et al.*, 1993;

James, *et al.*, 1991). The term "μ-selective opioid" refers to a drug that has a high affinity

for the μ-opioid receptors found throughout the neuroaxis and periphery. The other two

recognized opioid receptors, (*delta*) and (*kappa*), are also found within the neuroaxis

as well as the periphery. These three types of opioid receptors have different

distributions, agonists, antagonists, as well as functions with nominal overlapping of each

of those variables. Receptor agonists at the μ-receptors include morphine and the

phenylpiperidines. Desired effects of the μ-receptor agonists include blockade of

mechanical, thermal, and chemical nociceptive stimuli (Dhawan, *et al*., 1996). Agonism

of the μ-receptor has a stronger positive correlation with analgesia than with the other

known opiate subtypes (Thorpe, 1984). Other effects of these agonists include depression

of the following functions: respiration, cardiovascular, gastrointestinal motility, learning

and memory, thermoregulation, immune response, and, notable for this study,

psychomotor activity. Antagonists at μ sites include naloxone and naltrexone. Naloxone

is the more selective of the two antagonists at the μ-receptor (Dhawan, *et al*., 1996).

<div align="center">Fentanyl</div>

Figure 1

Molecular Structure of Fentanyl.
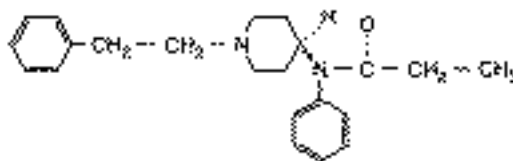
Fentanyl (Figure 1) was synthesized by Janssen Pharmaceuticals in 1960 in the

quest for an opiate with greater potency and safety (Willens & Myslinski, 1993). It has

approximately 100 times the potency of morphine along with greater lipophilicity. This

greater lipid solubility likewise results in an onset of action that is more rapid than that of

morphine. Termination of action is determined by rapid redistribution to inactive tissues

such as the lungs, fat, and muscle for subsequent metabolism primarily in the liver

(Murphy, Hug, & McClain, 1983). The lungs, in fact, serve as a large reservoir for

fentanyl. Over 75% of a dosage of fentanyl is sequestered in lungs with first pass uptake

(Roerig, *et al*., 1987). Fentanyl is metabolized through first-order kinetics in the liver

primarily by dealkylation, hydroxylation, and amide hydrolysis to inactive metabolites

(McClain & Hug, 1980). The problem with this method of elimination is that with a

repeated or continuous infusion, the inactive tissues become saturated and act as a

reservoir for the drug. This prolongs the amount of time before complete metabolism

occurs for total deactivation of the drug (Shafer & Varvel, 1991).

<div align="center">Remifentanil</div>

Figure 2

Molecular Structure of Remifentanil.
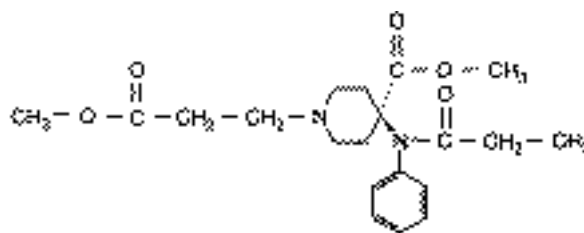
Remifentanil (Figure 2) is the latest in the family of the phenylpiperidines. It was

first synthesized and then described in 1991 (Feldman, *et al.*). The impetus for its

creation was to introduce a new ultra-short acting μ-opioid agonist with more predictable

pharmacokinetics (Glass, Kapila, Muir, Herman, & Shiraishi, 1993). It has pure μ-

receptor affinity like its predecessors as demonstrated with competitive antagonism by

naloxone (Amin, *et al.*, 1993).

The major difference between remifentanil and fentanyl involves

pharmacokinetics. Recall that fentanyl's termination of action is dependent upon

redistribution and liver metabolism. Remifentanil's termination of action is accomplished

by nonspecific blood esterases (Feldman, *et al.*, 1991). This is similar to esmolol, a

selective $_1$ antagonist (Lowenthal, *et al.*, 1985). This is possible due to the attachment of

a methyl ester group onto the N-acyl side chain of the piperidine ring. This esterification

results in a structure that is highly susceptible to hydrolysis by the ubiquitous esterases.

Further, this side chain is not a substrate for pseudocholinesterase, plasma cholinesterase,

and therefore its metabolism and clearance are not affected by pseudocholinesterase

abnormalities or anticholinergic agents (Stiller, *et al.*, 1995; Selinger, Nation, & Smith,

1995). Also, in contrast to fentanyl, there are no tissue reservoirs for remifentanil.

Clinically, these differences have important implications which are best understood when

comparing Context Sensitive Half-Times (CSHT) (Figure 3) (Burkle, Dunbar, & Van

Aken*,* 1996).

Context Sensitive Half-Time

Figure 3

Context Sensitive Half-Time for Fentanyl and Remifentanil.

Duration of Infusion (min .
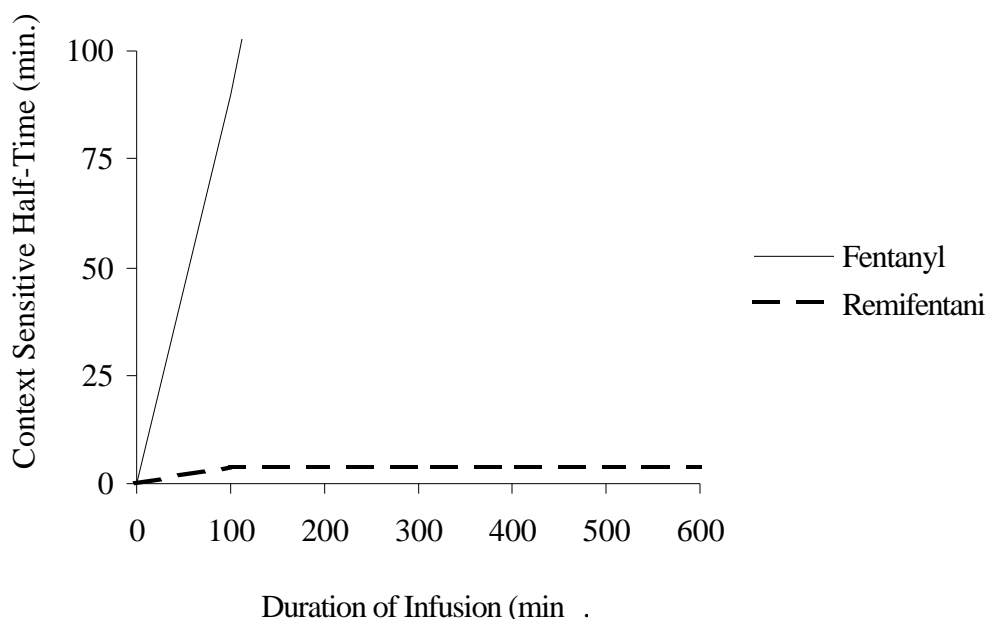
Context Sensitive Half-Time (CSHT) is a computer simulated estimation of the time to a 50% decrease in effective site concentration after termination of infusion. The "effective site" is the μ-receptor. Essentially, this measurement replaces termination half-life, $t_{1/2}$, which until recently was the best measurement available to assist in predicting a drug's duration of action.

Termination half-life ($t_{1/2}$) is dependent upon volume of distribution (Vd) and drug clearance (CL) (see Equation 1):

Equation 1

Termination Half-Life ($t_{1/2}$).

$$t_{1/2}= \frac{0.7 \text{ x Vd}}{\text{CL}}$$

"0.7" is a constant. It is an approximation of 0.693, the natural logarithm of two. Volume of distribution (Vd) is the ratio of the amount of drug in the body to the concentration of drug in blood or plasma. Clearance (CL) is a ratio, as well. It shows the

relationship between the rate of elimination of a drug by all routes, *e.g.*, renal or hepatic, to the concentration of drug in intracellular and/or extracellular fluid. This measurement of termination half-life ($t_{1/2}$) is accurate provided that there is only one body compartment involved in a drug's absorption. Erroneous results follow, however, when there are multiple body compartments that serve as reservoirs for a drug. This is the case with agents, such as fentanyl, which are dependent upon redistribution from blood or plasma for termination of action (Holford & Benet, 1992).

The Context Sensitive Half-Times (CSHT) shown in Figure 3 reveal three facts: first, remifentanil has a very abbreviated Context Sensitive Half-Time; second, its CSHT is independent of length of infusion; lastly, its CSHT profile is very different from that of fentanyl. Clinically, this implies that remifentanil has a very predictable duration of action and, further, it is easily titratable for desired effect (Westmoreland, Sebel, Hug, Hoke, & Muir, 1993a). In contrast, fentanyl's offset of action would be less predictable and more difficult to titrate. The short Context Sensitive Half-Time of remifentanil has been replicated in human subjects with clinical trials (Westmoreland, Sebel, Hug, Hoke, & Muir, 1993a; Dershwitz, *et al.*, 1995; Kapila, *et al.*, 1995).

<u>Significance of the Problem</u>

Nurse anesthetists can utilize this difference in pharmacokinetics to assist both their patients and the institution where they practice. The potential benefit to the patient involves helping him meet his postoperative self-care needs more quickly with shorter-acting drugs. The possible benefit that may be realized by the institution with a shorter-acting drug, *i.e.*, remifentanil, would be a savings in cost in the postanesthesia care unit (PACU). This follows the logic that shorter-acting drugs decrease time to discharge. This

argument was recently disputed, however, by Dexter and Tinker (1995). Their study

showed that the cost benefit of shorter-acting drugs was negligible. Personnel costs, not

supplies or materials, represented the largest part of PACU expenses. Staffing patterns

have remained static due to operating room schedules and minimal PACU staffing

requirements. This is in spite of the advent of shorter acting drugs. A subsequent

comment by Dexter to the initial report, however, did state that costs may be reduced by

shorter-acting drugs in some instances (Hagan & Dexter,1995). Examination of this

hypothesis is, however, beyond the scope of this research.

<div align="center">Problem Statement</div>

Impaired psychomotor recovery from general anesthesia in outpatient surgery

delays discharge of patients from the post-anesthesia care unit (PACU).

<div align="center">Hypothesis</div>

Patients recovering from a remifentanil and volatile based anesthetic will have a

more rapid recovery of psychomotor functioning postoperatively than patients receiving

fentanyl and volatile based anesthetic.

II: LITERATURE REVIEW

A review of literature is useful in comparing and contrasting these two opioids from the phenylpiperidine family. Of note is the fact that, to date, there have been no published studies comparing psychomotor recovery status post administration of these two phenylpiperidines in humans.

Pharmacodynamics

Pharmacodynamically, remifentanil and fentanyl are slightly different. Remifentanil has a p a of 7.1 as opposed to fentanyl's p a of 8.4. This results in remifentanil having a higher percentage of un-ionized drug at physiologic pH, 67% compared to 9% for fentanyl. This leads to increased lipid solubility and blood brain barrier permeability. In keeping with this, remifentanil has a more rapid onset of action than fentanyl. One way to assess this is through comparing their respective onset half-lives ($t_{1/2ke0}$). The $t_{1/2ke0}$ is ascertained through the spectral edge frequency of an electroencephalogram (EEG). It is the equilibration half-time between drug effect and arterial drug concentration. Remifentanil has a $t_{1/2ke0}$ of 1.3 minutes. Fentanyl has a $t_{1/2ke0}$ of 6.6 minutes (Lemmens, 1995).

Remifentanil and fentanyl have slightly different potencies, as well. Egan, Muir, Stanski, and Shafer (1996) demonstrated a positive correlation between EEG activity and analgesic potency. Remifentanil requires a steady state concentration of 14.7 µg/L to cause half the maximal EEG slowing. Fentanyl requires a steady state concentration of 8.1 µg/L (Lemmens, 1995). In experiments with rats, however, remifentanil appears to be more potent. The ED_{100} dose for loss of righting with remifentanil is 0.020mg/kg/min.

and for fentanyl the dose is 0.035 mg/kg/min. (Lozito, LaMarca, Dunn, & Jerussi, 1994). "Righting" is the function of the cord righting reflex found in quadrapeds such as rats. This reflex signifies that complex functions necessary for coordination of posture are intact (Guyton & Hall, 1996).

Both phenylpiperidines have similar effects on the MAC (minimum alveolar concentration) of volatile anesthetics. The MAC of a volatile anesthetic is defined as the concentration of that volatile anesthetic at one atmosphere which prevents skeletal muscle movement in response to a supramaximal painful stimulus, such as surgical incision, in 50% of patients (Merkel & Eger, 1963). A 50% reduction in MAC is realized with isoflurane when the plasma concentration of remifentanil is 1.37 ng/ml (Lang, *et al*., 1996). Fentanyl requires a slightly higher plasma concentration, 1.67 ng/ml, to attain this same reduction in isoflurane MAC (McEwan, *et al*., 1993).

Remifentanil and fentanyl cause the same adverse effects to varying degrees which are mediated at the μ-receptor. With rapid infusion of large doses of either drug, there is myocardial depression manifested as hypotension, mild bradycardia, and dysrhythmias (Pitts, Palmore, Salmenpera, Kirkhart, & Hug, 1992; Sebel, Hoke, Westmoreland, Hug, Muir, & Szlam, 1995; Lemmens, 1995). This is largely caused by stimulation of the vagal nucleus of the medulla (Laubie, Schmitt, & Vincent, 1979). Muscle rigidity is another adverse effect shared by these drugs. The mechanism of action of this is unclear, but stimulation of μ-receptors in the caudate nucleus may play a role (Benthuysen, Smith, Sanford, Head, & Silver, 1986). This rigidity is plasma concentration dependent and can be seen with induction doses. Clinically, this adverse

effect results in patients that are difficult to ventilate (Streisand, *et al*., 1993; Lemmens, 1995). Both drugs also produce respiratory depression in spontaneously breathing patients. Like other opiates, they decrease the response of chemoreceptors in the medulla to increases in carbon dioxide (Becker, Paulson, Miller, Severinghaus, & Eger, 1976; Egan, *et al*., 1993). Also, both opioids directly trigger the emetic zone located in the area postrema in the floor of the fourth ventricle which might result in nausea and vomiting (Egan, *et al*., 1993; Ding, Fredman, & White, 1993).

Of note is the fact that neither fentanyl nor remifentanil cause an increase in serum histamine levels. Phenylpiperidines, unlike morphine, do not trigger the release of histamine (Rosow, Moss, Philbin, Savarese, 1982; Westmoreland, Sebel, Hug, Hoke, & Muir, 1993b; Sebel, *et al*., 1995).

<div align="center">Pharmacokinetics</div>

As mentioned in Chapter One, there are many pharmacokinetic differences between remifentanil and fentanyl. One notable example is the extensive first-pass uptake of fentanyl into the lungs. Approximately 75% of fentanyl is sequestered in the lungs (Roerig, *et al.,* 1987). Remifentanil does not appear to undergo this same first-pass effect in the lungs (Duthie, *et al*., 1995). Further, fentanyl is dependent on the liver for metabolism to inactive metabolites, *i.e.*, norfentanyl and desproprionylnorfentanyl, which are excreted in urine and bile over 72 hours (McClain & Hug, 1980). Remifentanil, on the other hand, undergoes de-esterification by ubiquitous esterases to a carboxylic acid metabolite, GI90291, which is excreted in the urine. The metabolite GI90291 has a $t_{1/2}$ (termination half-life) of 1.5 to 2 hours and $1/4600^{th}$ the potency of remifentanil in dogs (Westmoreland, *et al.*, 1993a).

Fentanyl has a $t_{1/2}$ of 3 to 3.65 hours at clinically relevant doses. This prolonged

$t_{1/2}$ reflects fentanyl's lipophilicity (Murphy, *et al.*, 1983). Remifentanil has a $t_{1/2}$ of 10

minutes at clinically relevant doses. However, as stated previously, Context Sensitive

Half-Time may actually be a better measure of termination of action with these opioids.

Upon stopping a continuous 4-hour infusion of fentanyl, 262.5 minutes were required for

a 50% reduction in effect site concentration. In contrast, there was a 50% reduction in

effect site concentration within 3.65 minutes upon stopping a 4-hour infusion of

remifentanil (Westmoreland, *et al.*, 1993b).

Interestingly, physical traits such as age, weight, and gender may have no

significant pharmacokinetic bearing with a remifentanil infusion (Egan, Billard, Barr,

Gambus, & Hermann, 1995; Westmoreland, *et al.,* 1993a). Reports of this have been

conflicting, however (Minto, *et al*., 1997). Age does appear to play a role in fentanyl

pharmacokinetics as volumes of distribution increase with age (Singleton, Rosen, &

Fisher, 1988).

<u>Psychomotor Recovery Implications</u>

Although no studies have compared the psychomotor recovery in humans of these

two drugs, a study by La Marca, Lozito, and Dunn (1995) did compare cognitive and

electroencephalographic (EEG) recovery using an animal model. This study

demonstrated the relative equipotency of the two opioids using the ED_{150} for loss of

righting (LOR). The ED_{150} dosage was extrapolated with drug-naive rats by means of

linear regression analysis based on the dose response curves for LOR of each of the

opioids. The ED_{150} for remifentanil was 0.04 mg/kg IV bolus. Fentanyl had an ED_{150} of

0.06 mg/kg IV bolus. As anticipated by their respective onset half-lives, remifentanil had

a more rapid onset of action as determined by EEG, 0.11+/-0.02 minutes as compared to

0.27+/-0.04 minutes for fentanyl. Duration of loss of righting after a bolus of remifentanil

and fentanyl was 3.01 minutes and 13.34 minutes respectively. These findings may

correlate with similar psychomotor recovery in humans. The most profound finding was

the difference in length of time to cognitive recovery between these two agents.

Cognitive recovery was assessed by having the rats navigate a maze. Cognitive recovery

was manifested concurrently with return of righting for the rats receiving remifentanil.

That was contrasted to a cognitive recovery for rats receiving fentanyl taking greater than

30 minutes after return of righting (LaMarca, *et al.*, 1995).

Psychomotor Recovery Assessment

A recently published article compared psychomotor recovery of remifentanil and

alfentanil, another rapid-onset phenylpiperidine, in human subjects (Philip, *et al*., 1997).

In this study, psychomotor function was measured with both the Trieger Dot test and the

digit symbol substitution test. This study sampled subjects receiving total intravenous

anesthesia (TIVA) for outpatient laparoscopies. Upon evaluation of their results, the

Trieger Dot test was noted to be more sensitive to differences in psychomotor recovery

between the two agents.

The Trieger Dot test (see Appendix F) was utilized for this study, as well . This

tool has been used in numerous previous studies evaluating psychomotor functioning as

affected by fentanyl and other sedative agents (Gelfman, *et al*., 1979; Gupta, Kullander,

Ekberg, & Lennmarken, 1995; McClure, Brown, & Wildsmith, 1983; Philip, *et al.*,

1997). The Trieger Dot test is a modification of the Bender motor Gestalt test. It is

capable of providing statistically significant results upon the subject attaining stage II of

recovery. Results, however, are not always statistically significant 3 hours postoperatively. This limitation aside, the Trieger Dot test is inexpensive, easy to administer, and is free of practice effects (Gelfman, *et al*., 1979). Further, this tool's construct validity has been affirmed through the concurrent use of other psychomotor assessment tools such as the pursuit rotor task apparatus and p-deletion test (Gelfman, *et al.*, 1979; Gupta, *et al.*, 1995). The Trieger Dot test is available for public use.

The use of paper and pencil tests to assess psychomotor recovery has disadvantages and advantages when compared to other measurements of psychomotor functioning. Mood, age, circadian rhythm, or being deprived of glasses or a hearing aid may adversely affect a patient's performance. Also, the sensitivity of these tests may be questionable given the patient's perception of their relative importance or lack thereof (Lichtor, 1997). However, tests that measure direct psychomotor functions, *e.g*., walking, may be insensitive to small changes in performance and may be influenced by a prior level of mastery (Herbert, 1978).

The stated hypothesis is based upon this review of literature and Orem's self-care model of nursing. Previous studies suggest that the pharmacokinetics of the respective drugs will demonstrate the hypothesis to be a valid one.

III: CONCEPTUAL FRAMEWORK

This study is based upon Dorothea Orem's conceptual model of nursing (1995).

With this model, nursing is defined as a practical science. As a practical science, nursing

is concerned with knowledge as well as with things that are doable. Nurse anesthesia is

an extension of the practical science of nursing. Four different concepts serve to focus a

nurse's actions within this model: the person requiring nursing; the product of nursing;

phases and units of action; and an understanding of good.

A person in day-to-day life possesses the capabilities to complete his own

universal self-care requisites, *e.g.*, prevention of hazards to life. This equilibrium is

disturbed with surgery, however. The person, patient, requires nursing preoperatively,

intraoperatively, and postoperatively as their ability to accomplish their self-care

requisites is impeded. Preoperatively, the patient is required to alter his self-care routine

secondary to medical orders such as bowel preparation and NPO orders. Intraoperatively,

self-care requisites as basic as breathing may need to be assisted. Postoperatively, the

patient will have health-deviation self-care requisites which include impaired

psychomotor functioning. Impaired psychomotor functioning deals directly with the

patient's ability to accomplish his self-care needs independently.

The nurse's role within this theory is that of a care agent. Optimally, one of the

nurse's objectives is to ensure that the patient's period of dependent-care is as brief as

possible. Consistent with that, nurses as anesthetists seek to expedite recovery of their

patient's psychomotor functioning. The nurse anesthetist's task is to understand the

physical deficit, pharmacologic in origin, and apply that understanding to minimize the resultant self-care limitations.

With deliberate appreciation of the components of a goal, *e.g.*, surgical anesthesia, a nurse's understanding of that goal will be improved upon. Phases and units of action serve as subsets of decision-making and meaningful effort within the overall goal. Phases of action start with assessment followed by plan-making, implementation, and, lastly, evaluation. Evaluation initiates the sequence once more from the period of plan-making. Phases of action for surgical anesthesia extend from the nurse anesthetist's first contact with the patient to a time when anesthetic sequelae are no longer of concern. Units of action, on the other hand, deal with isolated decisions and subsequent actions. The nurse anesthetist's choice and implementation of an anesthetic utilizing a particular opioid is considered a unit of action.

Implicit to the concept of nursing and self-care is the objective of understanding and accomplishing good. Good at its simplest is the opposite of bad. For the purpose of this study, good is outcome oriented. Good is a rapid return of psychomotor functioning in the postoperative period.

This research is experimental. The independent variable is the use of an opioid, fentanyl or remifentanil, for balanced anesthesia. The dependent variable is the relative speed of psychomotor functioning recovery postoperatively after utilizing either fentanyl or remifentanil.

IV: METHODOLOGY

The design of this experimental study as well as the methods employed in testing the stated hypothesis will be outlined in this chapter. It was hypothesized that patients recovering from a remifentanil and volatile based anesthetic would have a more rapid recovery of psychomotor functioning postoperatively than patients receiving a fentanyl and volatile based anesthetic.

Study Sample

The study was conducted at Malcolm Grow Medical Center, Andrews Air Force Base, Maryland, during the months of January and March 1998. The targeted population were patients undergoing outpatient surgery with a balanced anesthetic using an opioid as the primary analgesic agent. Any outpatient surgery lasting up to approximately one to two hours was accepted for study inclusion. Sampling criteria were intended to limit variables which might alter the validity of the study. For example, patients with ongoing psychiatric disease, patients undergoing hand surgery on their dominant hand, or patients with uncorrected impaired vision were excluded from the study. In an attempt to enlarge the sample size, the principal investigator trained two other nurse anesthesia graduate students to conduct the study as proxies. Training of these student anesthetists consisted of having them read a written abstract as well as hearing a briefing about the study and a demonstration of the Trieger Dot test by the principle investigator. The first 23 subjects to which the principal investigator, or a proxy, were assigned who met the inclusion criteria and who gave consent for admission to the study were sampled. The subjects were randomly assigned to either the fentanyl or remifentanil group. Assignment to either

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group was randomized by assigning prospective subjects a number from 1 to 30. The numbers 1 through 30 were randomly selected by writing the numbers 1 through 30 on individual pieces of paper and then selecting them from a bowl. The first 15 numbers withdrawn were designated as being in the fentanyl group and the remaining numbers were designated to the remifentanil group.

The sampled subjects included both genders to increase the generalizability of results. Subjects ranged from 22 to 67 years of age. Patients with psychiatric disorders, non-English speaking patients, or patients receiving agents that might have altered mentation, *e.g.,* antipsychotics and benzodiazepines, were excluded from the study. Subjects requiring prosthetic devices such as corrective glasses or hearing aids utilized these devices throughout the interview period as well as with each administration of the Trieger Dot test. Subjects who were physically unable to complete the Trieger Dot test preoperatively, *e.g*., subjects with severe rheumatoid arthritis, or who would be unable to complete the test postoperatively, e.g., dominant hand surgery, were excluded from the study.

A record review of prospective subjects was completed prior to the initial interview by the investigator. At this point, patients meeting inclusion criteria underwent a scripted interview in the preoperative holding area (see Appendix D). Willing patients were enrolled in the study once they had signed a consent (see Appendices B & C). Subjects received a copy of the consent upon discharge from the post anesthesia care unit (PACU).

Trieger Dot Administration

The Trieger Dot test was administered by the investigator twice preoperatively in the holding area after the subject's consent to join the study was obtained. These initial tests were intended to establish a baseline score for each subject as well as to help establish the tool's test-retest reliability. Postoperatively, the test was given in the post anesthesia care unit (PACU) once the subject's PACU nurse determined that the patient had attained an Aldrete score of eight or greater. This is Stage II of recovery, "Early Recovery". Recall from Chapter One that Stage II of recovery is usually attained within 15-60 minutes postoperatively. At this point, the subject is awake and alert, hemodynamically stable, can maintain their own airway, and has return of their protective reflexes. After this initial test, subjects were then tested again every 15 minutes until discharge. All subjects were discharged from PACU before the 60-minute test could be obtained. A scripted explanation of the test was given by PACU nurses and technicians with each administration of it (see Appendix D). Training of PACU nurses and technicians for administration of the Trieger Dot test consisted of having them read a written abstract as well as hearing a briefing about the study with a demonstration of the test by the principle investigator. Most subjects were in the sitting position for each administration of the test. Any exceptions to sitting position were noted on the test form. Subjects were given 30 seconds to complete the test each time.

Scoring of the Trieger Dot test was done on a single-blinded basis by one scorer. The scorer had no prior knowledge of the subjects. All Trieger Dot tests were assessed by the same scorer successively over a one hour period. Score was determined by the

number of dots missed by the subject. Thus, the lower a subject's score, the better the psychomotor ability as determined by the Trieger Dot test.

Anesthetic Protocol

The principal investigator, under supervision of a qualified anesthesia provider, or a fellow nurse anesthesia student, provided anesthesia for each of the subjects. The protocol varied between the two study groups in accordance with the differences in pharmacokinetics (see Appendix G1 and G2).

Protection of Human Rights

Prior to joining the study, each subject received a standardized explanation of the study as well as an opportunity to ask the investigator specific questions regarding its administration and purpose. Willing subjects signed a consent witnessed by a person not participating in the study. Subjects were provided with a copy of the consent by the post anesthesia care unit (PACU) personnel upon discharge from PACU.

Assumptions

1. Subjects cooperated to the fullest extent of their abilities.

2. Early postoperative recovery of psychomotor function is desirable.

Limitations

1. Drug reactions, patient attitudes, and surgeons' support of the research were

variables beyond the investigator's control.

2. Only one clinical site was sampled. This may possibly limit the generalizability

of the results.

3. Premedication with midazolam, may have affected subjects differently and

could have contributed to postoperative drowsiness.

4.   Variety in case procedure, length and amount of anesthesia required may have significantly influenced values of dependent variables.

V: DATA ANALYSIS

Analysis of data was first directed towards ascertaining whether the subjects were adequately randomized into separate groups, remifentanil or fentanyl. Test-retest reliability of the Trieger Dot test was assessed, as well. Lastly, the hypothesis was tested. All statistical analysis was done through SPSS, version 8.0 for Windows.

Randomization

Assessment of randomization between groups revealed several key points. Using t-test for equality of means, there was no statistical significance between the two groups with regards to age ($p=0.6$), body mass index ($p=0.2$), or gender ($p=0.3$) with equal variances assumed. These variables were adequately randomized to preclude a skew. There was, however, a significant difference between length of anesthetic time means ($p=0.03$) when using t-test. The mean length of anesthetic time with remifentanil was 69.58 minutes with a standard error of the mean of 11.81. For fentanyl, the mean length of anesthetic time was 108.64 minutes with a standard error of the mean of 12.36.

Given the relatively small sample size, 23, randomization between groups for the four basic types of outpatient surgery appeared adequate (Table 1).

Table 1

Randomization Between Groups for Surgical Type.

Surgical Type	Remifentanil	Fentanyl	Total
gynecological	1	2	3
ENT	5	5	10
laparoscopic	5	4	9
intraabdominal	1	-	1
Total	12	11	23

Because the pharmacokinetics of remifentanil and fentanyl are so different, comparison of the amount of drug administered is not an accurate measure of expected postoperative effect. Comparing the amount of fentanyl administered to the length of remifentanil infusion along with maintenance rate does give insight to the amount of narcotic required for these cases. Subjects in the fentanyl arm received on average 3.5 mcg/Kg (S.D. 1.9). Subjects in the remifentanil arm received on average a maintenance infusion of 0.24 mcg/Kg/minute (S.D. 0.14) for 70 minutes.

Time from discontinuation of anesthesia ("discontinuation of isoflurane") to when subjects achieved an Aldrete score of 8 ("T0"), which was determined by the post anesthesia care unit (PACU) RNs, was not significant ($p=0.44$) between the two groups (Table 2).

Table 2

Time Lapse from Discontinuation of Isoflurane to T0 (Minutes).

Group	*n*	Mean	S.D.
remifentanil	12	37.08	11.57
fentanyl	11	43.00	23.00
Total	23	39.91	17.79

Trieger Dot Test Score Groups

Once the Trieger Dot tests had been scored, raw scores were assessed statistically. When very marginal significance was noted, these scores were then sorted into three different score groups by assessing the distribution of raw scores over each administration of the test. Score groups were divided into bottom third score, 0-6 dots missed, middle third score, 7-14 dots missed, and high third score,15-34 dots missed. This was out of a possible 40 dots. The low score group was assigned the number one,

the middle score group two, and the high score group three. Thus, like the raw score, the lower a subject's score group, the better their psychomotor ability as determined by the Trieger Dot test.

<div align="center">Trieger Dot Test-Retest Reliability</div>

Trieger Dot test-retest reliability was assessed by having each subject complete the test twice preoperatively. The tests were given within 30 seconds of one another. Comparing means of the two preoperative testings for the 23 subjects yielded a Pearson's r of 0.76, a high correlation (Burns & Grove, 1993) that helps establish test-retest reliability of the instrument.

Likewise, Table 3 shows that prior to administration of the study protocol, subjects in both groups had comparable levels of psychomotor competence as determined by the Trieger Dot test.

Table 3

Trieger Dot Baseline Score Groups.

		N	Mean	S.D.
score group, first score	remifentanil	12	1.17	0.58
	fentanyl	11	1.00	0.00
	Total	23	1.09	0.42
score group, second score	remifentanil	12	1.08	0.29
	fentanyl	11	1.00	0.00
	Total	23	1.09	0.42

<div align="center">Trieger Dot Scores Repeated Measures</div>

Trieger Dot score groups were compared between the two groups in order to assess for disparity in psychomotor recovery. "T0", "T15", "T30", "T45" denote the time at which psychomotor functioning was assessed postoperatively. "T0" was the initial postoperative assessment, "T15" was the assessment 15 minutes subsequent to the initial assessment, and so on.

The score groupings at the second baseline testing had a high level of correlation (r=0.97) signifying similar levels of psychomotor competence between groups. However, this correlation between the remifentanil and fentanyl groups was not high, or significant, postoperatively -- at T0 r=0.25, T15 r=0.14, T30 r=0.49. Two subjects, both in the fentanyl group, were tested at T45. All subjects were discharged from the post anesthesia care unit (PACU) prior to T60 assessment.

Table 4 and Figures 4, 5, and 6 describe how each group scored postoperatively on the Trieger Dot test. The trend noted when assessing score group means is that the remifentanil subjects scored marginally, but not statistically significantly, better than their fentanyl counterparts within the first 15 minutes postoperatively. These remifentanil subjects, however, showed no improvement over time as evidenced by their mean T30 score being very similar to their T0 and T15 means. This may have been due to the fact that all remifentanil subjects received additional intraoperative, and sometimes postoperative, opioids to treat postoperative pain. The fentanyl subjects, on the other hand, did show improvement over time when the two T45 outliers were excluded.

Table 4

Trieger Dot Repeated Measures, Score Group Means.

Time		n	Mean	S.D.
score group, baseline second score	remifentanil	12	1.08	0.29
	fentanyl	11	1.09	0.30
score group T0	remifentanil	12	1.83	0.94
	fentanyl	11	2.27	0.79
score group T15	remifentanil	12	1.83	0.94
	fentanyl	9	2.33	0.71
score group T30	remifentanil	5	1.80	0.45
	fentanyl	5	1.60	0.55
score group T45	remifentanil	-	-	-
	fentanyl	2	2.50	0.71

Figure 4 represents a comparison of score group means over time postoperatively. Figures 5 and 6 display the distribution of the subjects at each postoperative testing. A comparable number of subjects were present for each postoperative testing excluding the T45 outliers in the fentanyl group.

Figure 4
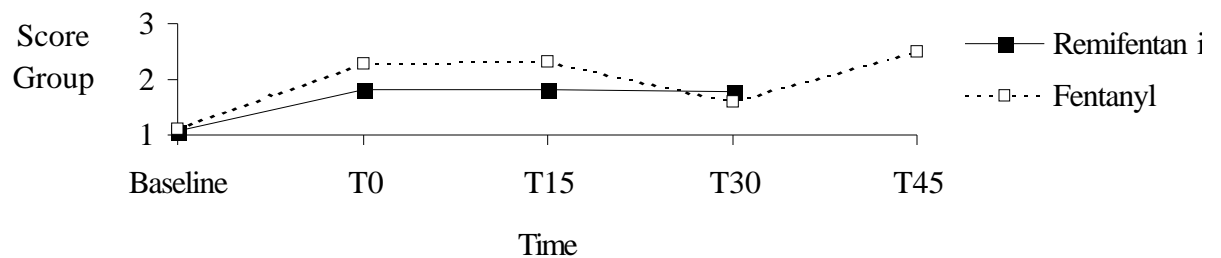
Trieger Dot Repeated Measures Score Group Means.

Figure 5

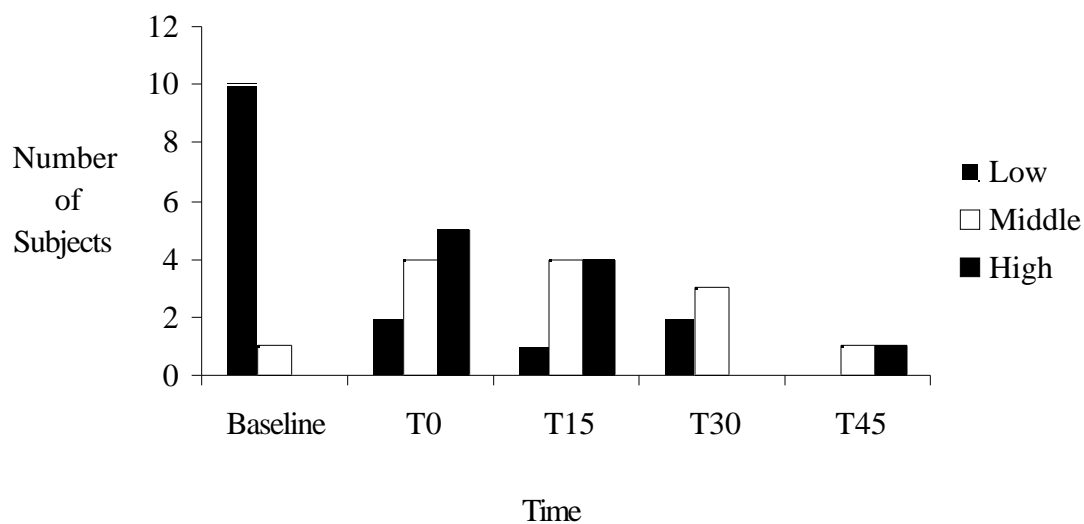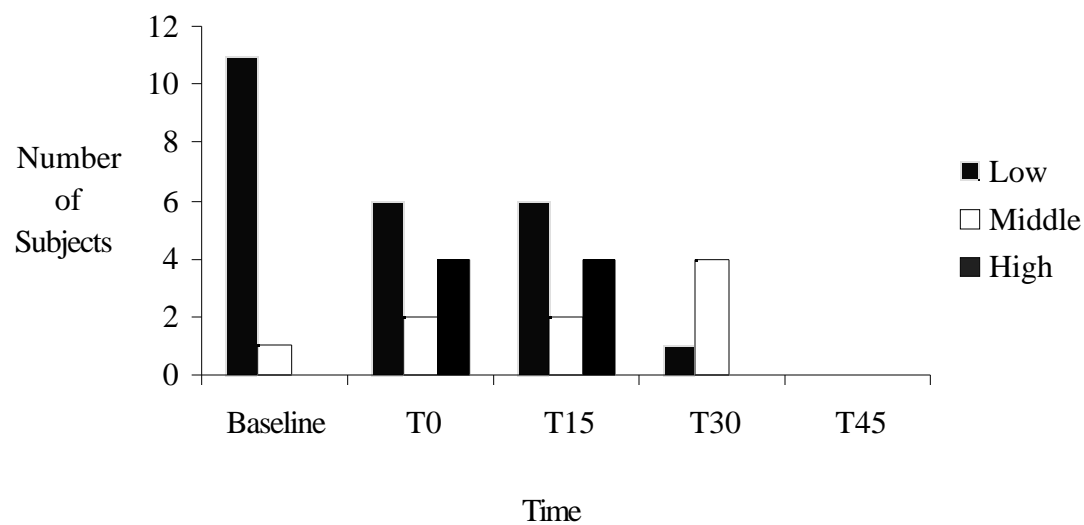Trieger Dot Repeated Measures Score Group Means, Fentanyl Subjects.

Figure 6

Trieger Dot Repeated Measures Score Group Means, Remifentanil Subjects.

VI: CONCLUSIONS

Most of the results of this study are open to interpretation. Some of the findings were expected, others were not. For example, the hypothesis for this study was that patients recovering from a remifentanil and volatile based anesthetic would have a more rapid recovery of psychomotor functioning postop

eratively than patients receiving fentanyl and volatile based anesthetic. This was not supported by the data. Reasons for this unexpected finding and others may lie within the design of the study.

The fact that there was no statistically significant difference in the lapse of time from the end of anesthesia to the attainment of an Aldrete score of eight may be the result of the effects of several confounding variables. These same variables may, in part, explain why the research hypothesis was rejected.

At the institution participating in this study, outpatient surgeries associated with postoperative pain great enough to require narcotic intervention do not routinely receive remifentanil intraoperatively. Anesthesia providers at this institution believe remifentanil is more useful when utilized in outpatient cases not associated with high levels of postoperative pain. This is due to the necessity of postoperative analgesics in these cases associated with high levels of postoperative pain. This was not fully appreciated when the study was designed. Intraabdominal and laparoscopic surgeries are two good examples of

outpatient surgeries sampled that are routinely conducted using an anesthetic with a longer lasting narcotic as an analgesic. To offset this anticipated postoperative pain in the remifentanil group, subjects received an increasing amounts of morphine. Morphine (0.1 mg/Kg) was given intraoperatively and postoperatively for patients in both groups. Demerol was given postoperatively only in the post anesthesia care unit (PACU) to patients in both groups, as well. Unfortunately, the principal investigator was not able to adequately monitor the amount of postoperative narcotic analgesics required for each subject. This factor almost certainly influenced study results.

It appears that subjects in the remifentanil group requiring a PACU admission of at least 15 minutes reached a plateau in their psychomotor recovery which remained static through their T30 testing. Over a 30 minute time span, these subjects failed to improve their psychomotor scores.

Subjects in the fentanyl group, in contrast, did have improved scores over a 30 minute time span. Although the remifentanil subjects scored lower through the T15 testing, the fentanyl subjects had lower scores at the T30 testing. It is speculated that this may have been due to the fact that remifentanil subjects required a greater amount of postoperative narcotic analgesics than the fentanyl subjects.

<div align="center">Implications</div>

The major implication of this study is that the use of remifentanil intraoperatively in outpatient cases requiring significant postoperative analgesic control is not associated with improved psychomotor recovery scores.

<div align="center">Future Studies</div>

Future studies comparing psychomotor recovery between these two opioids should address the issues of homogeneity of the types of outpatient surgery. Although the research hypothesis was rejected, it is possible that a study including only surgeries with mild postoperative pain would reflect the predicted differences in psychomotor recovery. Additionally, collection of data about preoperative anxiolytics and monitoring of postoperative pain interventions would improve the study design, and further validate one aspect of Orem's conceptual model—ensuring that patients' periods of dependent-care are as brief as possible.

VI: REFERENCES

American Hospital Association Hospital Statistics: 1994-95 ed.. 1994. Chicago: American Hospital Association.

Amin, H. M., Sopchak, A. M., Esposito, B. F., Graham, C. L., Batenhorst, R. L., & Camporesi, E. M. (1993). Naloxone reversal of depressed ventilatory response to hypoxia during continuous infusion of remifentanil. Anesthesiology, 79 (3A), A1203.

Baker, P. J. (1994). Under the influence: Perioperative considerations in patients on street drugs and alcohol. CRNA, 5 (1), 14-19.

Becker, L. D., Paulson, B. A., Miller, R. D., Severinghaus, J. W., & Eger, E. I. (1976). Biphasic respiratory depression after fentanyl-droperidol or fentanyl alone used to supplement nitrous oxide anesthesia. Anesthesiology, 44 (4), 291-96.

Beck, A.T., Feshbach, S., & Legg, D. (1962). The clinical utility of the digit symbol test. Journal of Consulting and Clinical Psychology, 26 (3), 263-68.

Benthuysen, J. L., Smith, N. T., Sanford, T. T., Head, N., & Silver, H. (1986). Physiology of alfentanil-induced rigidity. Anesthesiology, 64 (4), 440-46.

Burkle, H., Dunbar, S., & Van Aken, H. (1996). Remifentanil: A novel, short-acting, μ-opioid. Anesthesia & Analgesia, 83 (3), 646-51.

Burns, N., & Grove, S. K. (1993). Bivariate inferential data. In N. Burns and S. K. Grove, The Practice of Nursing Research: Conduct, Critique, and Utilization, (2nd ed.) (pp. 493-526). Philadelphia: W. B. Saunders.

Cashman, J. N., & Power, S. J. (1989). An evaluation of tests of psychomotor function in assessing recovery following a brief anaesthetic. Acta Anaesthesiologica Scandinavica, 33 (8), 693-7.

Chung, F. (1995). Recovery pattern and home-readiness after ambulatory surgery. Anesthesia & Analgesia, 80 (5), 896-902.

Dershwitz, M., Randel, G. I., Rosow, C. E., Fragen, R. J., Connors, P. M., Librojo, E. S., Shaw, D. L., Peng, A. W., & Jamerson, B. D. (1995). Initial clinical experience with remifentanil, a new opioid metabolized by esterases. Anesthesia & Analgesia, 81 (1), 619-23.

Dexter, F., & Tinker, J. H. (1995). Analysis of strategies to decrease postanesthesia care unit costs. Anesthesiology, 82 (6), 94-101.

Ding, Y., Fredman, B., & White, P. F. (1993). Use of ketorulac and fentanyl during outpatient gynecologic surgery. Anesthesia & Analgesia, 77 (2), 205-210.

Dhawan, B. N., Cesselin, F., Raghubir, R., Reisine, T., Bradley, P. B., Portoghese, P. S., & Hamon, M. (1996). International union of pharmacology-XII: Classification of opioid receptors. Pharmacological Reviews, 48 (4), 567-92.

Dripps, R. D., Lamont, A., & Eckenhoff, J. E. (1961). The role of anesthesia in surgical mortality. The Journal of the American Medical Association, 178 (3), 261-66.

Duthie, D. J. R., Muir, K. T., Baddoo, H. H. K., Doyle, A. R., Stevens, J. J. W. M., Kirkham, A. J. T., Gupta, S. K., Frazer, N. M., Archer, S., Navapurkar, V. A., & Park, G. R. (1995). Remifentanil is not metabolized by the lung. Anesthesiology, 83 (3A), A324.

Egan, T. D., Billard, V., Barr, J., Gambus, P., & Hermann, D. J. (1995). Gender has no effect on the pharmacodynamics of remifentanil. Anesthesiology, 83 (3A), A325.

Egan, T. D., Lemmens, H. J. M., Fisett, P., Hermann. D. J., Muir, K. T., Stanski, D. R., & Shafer, S. L. (1993). The pharmacokinetics of the new short-acting opioid remifentanil (GI87084B) in healthy adult male volunteers. Anesthesiology, 79 (5), 881-92.

Egan, T. D., Muir, K. T., Stanski, D. R., & Shafer, S. L. (1996). The EEG versus clinical measures of opioid potency: Defining the EEG-clinical potency fingerprint with application to remifentanil. Anesthesiology, 85 (3A), A349.

Feely, T. W., & Botz, G. H. (1997). Factors influencing choice of anesthetic technique. In P. F. White (Ed.), Ambulatory Anesthesia and Surgery (pp. 190-97). London: W. B. Saunders.

Feldman, P. L., James, M. K., Brackeen, M. F., Bilotta, J. M., Schuster, S. V., Lahey, A. P., Lutz, M. W., Johnson, M. R., & Leighton, H. J. (1991). Design, synthesis, and pharmacological evaluation of ultrashort to ultralong-acting opioid analgetics. Journal of Medical Chemistry, 34 (7), 2202-8.

Gelfman, S. S., Gracely, R. H., Driscoll, E. J., Wirdzek, P. R., Butler, D. P., & Sweet, J. B. (1979). Comparison of recovery tests after intravenous sedation with diazepam-methohexital and fentanyl. Journal of Oral Surgery, 37 (5), 391-97.

Glass, P. S. A., Kapila, A., Muir, K. T., Herman, D. J., & Shiraishi, M. (1993). A model to determine the relative potency of *mu* opioids: Alfentanil versus remifentanil. Anesthesiology, 79 (3A), A378.

Gottlieb, G. L., Corcos, D. M., Jaric, S., & Agarwal, G. C. (1988). Practice improves even the simplest movements. Experimental Brain Research, 73 (2), 436-40.

Green, G., & Jonsson, L. (1993). Nausea: The most important factor determining length of stay after ambulatory anesthesia. A comparative study of isoflurane and/or propofol technique. Acta Anaesthesiologica Scandinavica, 37 (8), 742-46.

Griffith, H. R., & Johnson, G. E. (1942). The use of curare in general anesthesia. Anesthesiology, 3 (4), 418-20.

Gupta, A., Kullander, M., Ekberg, K., & Lennmarken, C. (1995). Assessment of recovery following day-case arthroscopy. Anaesthesia, 50 (11), 937-42.

Guyton, A. C., & Hall, J. E. (1996). Motor functions of the spinal cord: The cord reflexes. In A. C. Guyton and J. E. Hall (Eds.), The textbook of physiology, (9th ed.) (pp.685-96). Philadelphia: W. B. Saunders.

Hagan, M., & Dexter, F. (1995). Postanesthesia unit care costs. Anesthesiology, 82 (6), 1534-5.

Herbert, M. (1978). Assessment of performance in studies of anesthetic agents. British Journal of Anaesthesia, 50 (1), 33-8.

Holford, N. H. G., & Benet, L. Z. (1992). Pharmacokinetics & pharmacodynamics: Rational dose selection and the time course of drug action. In B. G. Katzung (Ed.), Basic and Clinical Pharmacology (6th ed.) (pp. 33-47). Norwalk, CT: Appleton & Lange.

James, M. K., Feldman, P. L., Schuster, S. V., Bilotta, J. M., Brackeen, M. F., & Leighton, H. J. (1991). Opioid receptor activity of GI 87084B, a novel ultra-short acting analgesic, in isolated tissues. The Journal of Pharmacology and Experimental Therapeutics, 259 (2), 712-18.

Kapila, A., Glass, P. S. A., Jacobs, J. R., Muir, K. T., Hermann, D. J., Shiraishi, M., Howell, S., & Smith, R. L. (1995). Measured context-sensitive half-times of remifentanil and alfentanil. Anesthesiology, 83 (5), 968-75.

Katzung, B. G. (1995). Cholinoceptor-blocking drugs. In B. G. Katzung (Ed.), Basic and clinical pharmacology (6th ed.) (pp.102-114). Norwalk, CT: Appleton & Lange.

La Marca, S. Lozito, R. J., & Dunn, R. W. (1995). Cognitive and EEG recovery following bolus intravenous administration of anesthetic agents. Psychopharmacology, 120 (4), 426-32.

Lang, E., Kapila, A., Shlugman, D., Hoke, J. F., Sebel, P. S., & Glass, P. S. A. (1996). Reduction of isoflurane minimal alveolar concentration by remifentanil. Anesthesiology, 85 (4), 721-8.

Laubie, M., Schmitt, H., & Vincent, M. (1979). Vagal bradycardia produced by microinjections of morphine-like drugs into the nucleus ambiguus in anesthetized dogs. European Journal of Pharmacology, 59 (3-4), 287-91.

Lemmens, H. J. M. (1995). Pharmacokinetic-pharmacodynamic relationships for opioids in balanced anesthesia. Clinical Pharmacokinetics, 29 (4), 231-42.

Lichtor, J. L. (1997). Recovery testing and evaluation. In P. F. White (Ed.), Ambulatory Anesthesia and Surgery (pp. 190-97). London: W. B. Saunders.

Liu, R., Barry, J. E. S., & Weinman, J. (1994). Effects of background stress and anxiety on postoperative recovery. Anaesthesia, 49 (5), 382-86.

Lowenthal, D. T., Porter, R. S., Saris, S. D., Bies, C. M. Slegowski, M. B., & Staudacher, A. (1985). Clinical pharmacology, pharmacodynamics, and interactions with esmolol. American Journal of Cardiology, 56 (1), 14f-17f.

Lozito, R. J., La Marca, S. L., Dunn, R. W., & Jerussi, T. P. (1994). Single versus multiple infusions of fentanyl analogues in a rat EEG model. Life Sciences, 55 (17), 1337-42.

Lundy, J. S. (1942). Balanced anesthesia. In J. S. Lundy (Ed.) Clinical Anesthesia. Philadelphia: W. B. Saunders.

McClain, D. A., & Hug, C. C. (1980). Intravenous fentanyl kinetics. Clinical Pharmacology & Therapeutics, 28 (1), 106-14.

McClure, J. H., Brown, D. T., & Wildsmith, J. A. W. (1983). Comparison of the I.V. administration of midazolam and diazepam as sedation during spinal anaesthesia. British Journal of Anaesthesia, 55 (11), 1089-92.

McEwan, A. I., Smith, C., Dyar, O., Goodman, D., Smith, L. R., & Glass, P. S. A. (1993). Isoflurane minimum alveolar concentration reduction by fentanyl. Anesthesiology, 78 (5), 864-69.

Merkel, G., & Eger, E. I. (1963). A comparative study of halothane and halopropane anesthesia. Anesthesiology, 24 (3), 346-57.

Minto, C. F., Schnider, T. W., Egan, T. D., Youngs, E., Lemmens, H. J., Gambus, P. L., Billard, V., Hoke, J. F., Moore, K. H., Hermann, D. J., Muir, K. T., Mandema, J.

W., & Shafer, S. L. (1997). Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. <u>Anesthesiology, 86</u> (1), 10-23.

Murphy, M. R., & Hug, C. C., & McClain, D. A. (1983). Dose-dependent pharmacokinetics of fentanyl. <u>Anesthesiology, 59</u> (6), 537-40.

New classification of physical status (1963). <u>Anesthesiology, 24</u> (11), 11.

Newman, M. G., Trieger, N., & Miller, J. C. (1969). Measuring recovery from anesthesia-a simple test. <u>Anesthesia & Analgesia, 48</u> (1), 136-40.

Orem, D. E. (1995). <u>Nursing: Concepts of practice</u> (5th ed.). St. Louis: Mosby.

Pandit, S. K., & Green, C. R. (1994). General anesthetic techniques. <u>International Anesthesiology Clinics, 32</u> (3), 55-79.

Pandit, S. K., & Pandit, U. A. (1997). Phases of the recovery period. In P. F. White (Ed.), <u>Ambulatory Anesthesia and Surgery</u> (pp. 190-97). London: W. B. Saunders.

Philip, B. K., Scuderi, P. E., Chung, F., Conahan, T. J., Maurer, W., Angel, J. J., Kallar, S. K., Skinner, E. P., Jamerson, B. D., & the Remifentanil/Alfentanil Outpatient TIVA Group (1997). Remifentanil compared with alfentanil for ambulatory surgery using total intravenous anesthesia. <u>Anesthesia & Analgesia, 84</u>, (3), 515-21.

Pitts, M. C., Palmore, M. M., Salmenpera, M. T., Kirkhart, B. A., & Hug, C. C. (1992). Pilot study: Hemodynamic effects of intravenous GI 87084B (GI) in patients undergoing elective surgery. <u>Anesthesiology, 77</u> (3A), A101.

Roerig, D. L., Kotrly, K. J., Vucins, E. J., Ahlf, S. B., Dawson, C. A., & Kampine, J. P. (1987). First pass uptake of fentanyl, meperidine, and morphine in the human lung. <u>Anesthesiology, 67</u> (4), 466-72.

Rosow, C. E., Moss, J., Philbin, P. M., & Savaresse, J. J. (1982). Histamine release during morphine and fentanyl anesthesia. <u>Anesthesiology, 56</u> (2), 93-6.

Sebel, P. S., Hoke, J. F., Westmoreland, C., Hug, C. C., Muir, K. T., & Szlam, F. (1995). Histamine concentrations and hemodynamic responses after remifentanil. <u>Anesthesia and Analgesia, 80</u> (), 990-3.

Selinger, K. Nation, R. L., & Smith, G. A. (1995). Enzymatic and chemical hydrolysis of remifentanil. <u>Anesthesiology, 83</u> (3A), A385.

Shafer, S. L., & Varvel, J. R. (1991). Pharmacokinetics, pharmacodynamics, and rational opioid selection. <u>Anesthesiology, 74</u> (1), 53-63.

Singleton, M. A., Rosen, J. I., & Fisher, D. M. (1988). Pharmacokinetics of fentanyl in the elderly. British Journal of Anesthesia, 60 (6), 619-22.

Smith, I., White, P. F., Nathanson, N., & Gouldson, R. (1994). Propofol: An update on its clinical use. Anesthesiology, 81 (4), 1005-43.

Stiller, R. L., Davis, P. J., McGowan, F. X., Scierka, A., Gupta, S., & Muir, K. T. (1995). In vitro metabolism of remifentanil: The effects of pseudocholinesterase deficiency. Anesthesiology, 83 (3A), A381.

Stoelting, R. K. (1991). Opioid agonists and antagonists. In R. K. Stoelting (Ed.) Pharmacology & Physiology in Anesthetic Practice (2nd ed.). Philadelphia: J. B. Lippincott.

Streisand, J. B., Bailey, P. L., LeMaire, L., Ashburn, M. A., Tarver, S. D., Varvel, J., & Stanley, T. H. (1993). Fentanyl-induced rigidity and unconsciousness in human volunteers. Incidence, duration, and plasma concentration. Anesthesiology, 78 (4), 629-34.

Taber's cyclopedic medical dictionary (15th ed.) (1985). Philadelphia: F. A. Davis

Thorpe, D. H. (1984). Opiate structure and activity: A guide to understanding the receptor. Anesthesia & Analgesia, 63 (2), 143-51.

Turner, N., Scarpace, P. J., & Lowenthal, D. T. (1992). Geriatric pharmacology: Basic and clinical considerations. Annual review of Pharmacology and Toxicology, 32, 271-302.

Weldon, B. C., Watcha, M. F., & White, P. F. (1992). Oral midazolam premedication in children: Effect of time and adjunctive therapy. Anesthesia and Analgesia, 75 (1), 51-55.

Westmoreland, C., Sebel, P. S., Hug, C. C., Hoke, J. F., & Muir, K. T. (1993a). Pharmacokinetics of remifentanil (GI87084B) and its major metabolite (GI90291) in patients undergoing elective inpatient surgery. Anesthesiology, 79 (5), 893-903.

Westmoreland, C., Sebel, P. S., Hug, C. C., Hoke, J. F., & Muir, K. T. (1993b). Histamine levels and hemodynamic responses following remifentanil. Anesthesiology, 79 (3A), A111.

White, P. F. (1996). What is new in ambulatory anesthesia techniques. American Society of Anesthesiologists: 1996 Annual Refresher Course Lectures, 321.

White, P. F., & Shafer, A. (1988). Clinical pharmacology and uses of injectable anesthetic and analgesic drugs. In B. V. Wetchler (Ed.), <u>Problems in Anesthesia</u> (pp. 37-54). Philadelphia: J. B. Lippincott.

White, P. F., & Smith, I. (1994). Ambulatory anesthesia: Past, present, and future. <u>International Anesthesiology Clinics</u>, <u>32</u> (3), 1-16.

Willens, S. W., & Myslinski, N. R. (1993). Pharmacodynamics, pharmacokinetics, and clinical uses of fentanyl, sufentanil, and alfentanil. <u>Heart & Lung</u>, <u>22</u> (3), 239-51.

Woodbridge, P. D. (1957). Changing concepts concerning depth of anesthesia. <u>Anesthesiology</u>, <u>18</u> (4), 536-50.

Yogendran, S., Asokumar, B., Cheng, D., & Chung, F. (1995). A prospective randomized double-blinded study of fluid therapy on postoperative complications in ambulatory surgery. <u>Anesthesiology</u>, <u>77</u> (3A), A34.

VIII: APPENDICES

A. Thesis Milestones

B. Subject Consent

C. Revised Subject Consent

D. Script

E. Data Collection Form

F. Trieger Dot Test

G1. Remifentanil Group, Anesthetic Protocol

G2. Fentanyl Group, Anesthetic Protocol

H. Malcolm Grow Medical Center IRB Approval Letter

I. USUHS IRB Correspondence

J. USUHS IRB Approval Letter

APPENDIX A

THESIS MILESTONES

DATE COMPLETED   MILESTONE

Year 1 - Spring Semester

_____   1. Selected the research topic and developed the research question.

_____   2. Discussed the proposed research with the potential Thesis Advisory Committee Chair, John P. McDonough, CRNA, Ed.D..

_____   3. Formed advisory committee with John P. McDonough, CRNA, Ed.D. as chair and Eugene Levine, Ph.D. and Maura S. McAuliffe, CRNA, Ph.D. as members.

_____   4. Prepared the research proposal.

_____   5. Distributed the proposal to all Committee members.

_____   6. Arranged for the proposal defense meeting with all Committee members to be present and submitted the Thesis Proposal Defense Request form to the secretary of the Department of Nursing Research.

_____   7. Proposal defended.

Year 1 - Summer Semester

_____   8. Made revisions as needed, and redistributed the proposal to all the members of the committee.

Year 2 - Fall Semester

_____   9. Proposal defended.
_____   10. Approved proposal submitted to Department of Nursing Research.

_____   11. Submitted copies of approved proposal to Institutional Review Boards at USUHS and Malcolm Grow Medical Center.

           USUHS IRB approval   24 March 1998
           MGMC IRB approval   18 December 1997

_____   12. Conducted the research; analyzed the data; and wrote up the results, conclusions, and recommendations.

Year 2 - Summer Semester

_____   13. Submitted a draft of completed thesis to Committee Chair.

_____   14. Arranged for the thesis defense meeting with all Committee members present and submitted the Thesis Defense Request Form to the secretary of the Department of Nursing Research. First portion of the thesis defense is an open meeting and may be attended by other people; whereas the second portion is a closed examination attended by only Committee members.

           Thesis defense meeting 13 August 1998

_____   15. Submitted materials for audiovisuals to be used in the thesis defense to the USUHS Audiovisual Department a minimum of two weeks prior to the scheduled defense.

_____   16. Revisions made as necessary to the thesis in order to obtain the approval signatures of the Committee members.

_____   17. Submitted the completed thesis, original and three copies to the Office of the Dean of the GSN by August 31 for program completion in October.

APPENDIX B

SUBJECT CONSENT

Uniformed Services University of the Health Sciences
Bethesda, MD 20814
Malcolm Grow Air Force Medical Center, Andrews Air Force Base, MD 20762
SUBJECT INFORMED CONSENT FORM

Introduction

You are being asked to take part in a research study of Ultiva™ (remifentanil HCl), an opioid (a drug that prevents and/or relieves pain, like morphine) recently approved for marketing by the Food and Drug Administration (FDA) for use in general anesthesia during surgery. Approximately 30 patients will take part in this study at Malcolm Grow Air Force Medical Center (MGMC). The study will be under the direction of Dr. John P. McDonough, CRNA, Ed.D. and G. Ralph Moseley, Capt., USAF, SRNA, NC. Your participation in this study begins when you sign this consent form and ends prior to your discharge from the PACU (recovery room).

Purpose

The purpose of this study is to observe how people recover their psychomotor functions (eye-hand coordination) after general anesthesia with either fentanyl or remifentanil as the opioid used during their surgery. Fentanyl is an opioid that has been used since the 1960's. Remifentanil, on the other hand, has just recently gained approval for marketing from the FDA. This study will help anesthesia providers to understand this relatively new drug.

Procedures

Before you can take part in this study, your anesthesia provider will obtain your medical history and examine you to see if meet the requirements of the study. Once your anesthesia provider determines that you can take part in this study and you sign this form, you will be asked to complete a connect-the-dots test to measure your baseline level of performance.

All routine procedures for someone scheduled for surgery under general anesthesia will be followed while you are in this study, such as the placement of standard monitoring equipment and frequent monitoring of your heart rate and blood pressure.
If you take part in this study, you will receive propofol to put you to sleep. Propofol is one of the most commonly chosen drugs used to put people to sleep for surgical anesthesia. To help keep you asleep and free of pain, you will receive isoflurane (an anesthetic gas) and either fentanyl or remifentanil.

If you receive remifentanil, before the end of your surgery you will receive Toradol, a drug like Tylenol, to help prevent any pain which might occur after surgery.

Also, regardless of which opioid you receive, the site of your surgical incision will be injected with bupivicaine, a local anesthetic, before the end of your surgery to help prevent postoperative pain.

Once you are in the PACU (recovery room) and are stable and awake enough, you will be given the same connect-the-dots test which you took before your surgery. You will be asked to complete this same test every 30 minutes until you are discharged from the PACU.

All routine interventions will be taken to ensure that you are comfortable in the PACU after your surgery.

Benefits

Since Ultiva^{TM} is very short acting, it does not accumulate (the level of drug does not increase over time). The same cannot be said of fentanyl. If you receive Ultiva^{TM} , it may be easier for your anesthesia provider to control the depth of your anesthesia during surgery and it may result in a faster recovery from anesthesia. Regardless of whether you receive fentanyl or remifentanil, measures will be taken to treat any potential or actual postoperative pain and/or nausea/vomiting. The true extent of the benefits expected from remifentanil such as reduction in the amount of time you spend in the PACU are unknown. However, the information gained from your participation in this study may benefit future patients. No benefit, however, is guaranteed.

Risks

Ultiva^{TM} was extensively tested before it was studied in humans and was given to over 2800 healthy volunteers and patients in clinical studies before receiving FDA approval. No side effects other than those known to be associated with other opioids and routine general anesthesia have been found. These side effects can be prevented by giving you other medications before or along with the opioid. Remifentanil's effect goes away very rapidly. As a result, there is a risk of postoperative pain if you were not treated. However, you will receive a pain medication before you wake to prevent this. You will also receive whatever medicine you need to treat any pain you have after surgery.

Alternative Procedures

If you do not take part in this study, you also receive any one or more of the drugs used in this study (fentanyl, Ultiva^{TM} , propofol, and isoflurane) during your surgery, but your anesthesia provider would also have the choice of using other drugs.

Confidentiality

Precautions will be taken to keep study documents which identify you by name confidential. Your name will not appear on any documents from MGMC. It will be removed, if necessary.

Subject Rights

Your participation in this study is entirely voluntary and you may withdraw from the study at any time. Refusing to participate or withdrawing from the study will involve no penalty or loss of benefits you might otherwise receive nor will it effect the care that you receive while at MGMC. Your anesthesia provider may decide to end your participation in this study at any time, without your approval, if he/she feels it is in your best interest.

By signing this form, you are not waiving any of your legal rights.

Additional Information Required by AFI 40-401

Records of my participation in this study may only be disclosed in accordance with federal law, including the Federal Privacy Act, 5 U.S.C. 562a, and its implementing regulations. DD Form 2005, Privacy Act Statement-Health Care Records, contains the Privacy Act Statement for the records. Records may also be examined by the U.S. Food and Drug Administration.

The Department of Defense will provide medical care for DoD eligible members (active duty, dependents, and retired military) for physical injury or illness resulting from participation in this research. Such care may not be available to other research participants, except in the event of an emergency. Compensation may be available through judicial avenues to non-active duty research participants if they are injured. I understand that my entitlements to medical and dental care and/or compensation in the event of injury are governed by federal laws and regulations, and if I desire further information, I may contact Capt. G. Ralph Moseley or Dr. John P. McDonough.

In the event that an unanticipated event (clinical or medical misadventure) occurs during my participation in this study, I will be informed. If I am not competent at that time to understand the nature of the event, such information will be brought to the attention of my guardian or next of kin.
The decision to participate in this study is completely voluntary on my part. No one has coerced or intimidated me into participating in this program. I am participating because I want to. Capt. Moseley and/or Dr. McDonough have adequately any and all questions I have about this study, my participation, and the procedures involved. I understand that Capt. Moseley and/or Dr. McDonough will be available to answer any questions concerning procedures throughout this study. I understand that if significant new findings develop during the course of this study which may relate to my decision to continue participation, I will be informed. I further understand that I may withdraw this consent at any time and discontinue further participation in this study without prejudice to my

entitlements to care. I also understand that the investigator for this study may terminate my participation in this study if he feels this to be in my best interest.

<u>Answers to Questions</u>

If at any time you feel that you may have sustained a research-related injury, you may call Capt. G. Ralph Moseley, SRNA, NC at (301) 589-2971 day or night. You may also call Dr. John P. McDonough, CRNA, Ed.D. at (301) 295-6565 (day) or (301) 315-2338 (night). They will that you receive appropriate medical treatment. If at any time before, during, or after the study you have any questions about the study you may call Capt. Moseley and/or Dr. McDonough at one of the above numbers. If you have any questions about your rights as a research subject, you may call USUHS Director, Research Programs (301) 295-3303 or USUHS General Counsel at (301) 295-3028.

I have fully explained this research, including the risks and alternate treatments, to the subject _____. In my judgment, there was sufficient access to information, including risks and benefits, to make an informed decision to participate in this study.
Investigator's Signature: _____   Date: _____

Investigator's Name (Print): _____

I have read the above description of the research study. I have talked it over with the anesthesia provider, have been given the opportunity to ask questions, and have had those questions answered to my satisfaction. I have also been given a copy of this consent form.

I understand that my participation is entirely voluntary and that I may withdraw my consent at any time, without penalty. I know enough about the purpose, procedures, risks, and benefits of the research study to decide that I want to take part in it.
For Women Able to Bear Children: I understand that if I am pregnant or breast-feeding I may not take part in this study. I am not breast-feeding and to the best of my knowledge, I am not pregnant.

I willingly give my consent to take part in this study.

_____   _____
Patient's Signature   Date and Time

_____

Patient's Social Security Number

_____   _____
Witness' Signature   Date and Time

APPENDIX C

REVISED SUBJECT CONSENT

Uniformed Services University of the Health Sciences
Bethesda, MD 20814
Malcolm Grow Air Force Medical Center, Andrews Air Force Base, MD 20762
SUBJECT INFORMED CONSENT FORM

<u>Introduction</u>

You are being asked to take part in a research study of Ultiva™ (remifentanil HCl), an opioid (a drug that prevents and/or relieves pain, like morphine) recently approved for marketing by the Food and Drug Administration (FDA) for use in general anesthesia during surgery. Approximately 30 patients will take part in this study at Malcolm Grow Air Force Medical Center (MGMC). The study will be under the direction of Dr. John P. McDonough, CRNA, Ed.D. and G. Ralph Moseley, Capt., USAF, SRNA, NC. Your participation in this study begins when you sign this consent form and ends prior to your discharge from the PACU (recovery room).

Purpose

The purpose of this study is to observe how people recover their psychomotor functions (eye-hand coordination) after general anesthesia with either fentanyl or remifentanil as the opioid used during their surgery. Fentanyl is an opioid that has been used since the 1960's. Remifentanil, on the other hand, has just recently gained approval for marketing from the FDA. This study will help anesthesia providers to understand this relatively new drug.

Opioids reduce response to painful stimuli. Other effects of opioids are respiratory depression, nausea, vomiting, constipation, itching, sedation, and confusion.

Procedures

Before you can take part in this study, your anesthesia provider will obtain your medical history and examine you to see if meet the requirements of the study. Once your anesthesia provider determines that you can take part in this study and you sign this form, you will be asked to complete a connect-the-dots test to measure your baseline level of performance. You will again be asked to complete the test postoperatively once the PACU nurses determine that you are stable and capable of taking it. You will be asked to complete the test every 15 minutes from that point until you are discharged from the PACU. Your participation in the study is over upon your discharge from the PACU.

All routine procedures for someone scheduled for surgery under general anesthesia will be followed while you are in this study.

Confidentiality

Precautions will be taken to keep study documents which identify you by name confidential. Your name will not appear on any documents from MGMC. It will be removed, if necessary.

Subject Rights

Your participation in this study is entirely voluntary and you may withdraw from the study at any time. Refusing to participate or withdrawing from the study will involve no penalty or loss of benefits you might otherwise receive nor will it effect the care that you receive while at MGMC. Your anesthesia provider may decide to end your participation in this study at any time, without your approval, if he/she feels it is in your best interest.

By signing this form, you are not waiving any of your legal rights.

Additional Information Required by AFI 40-401

Records of my participation in this study may only be disclosed in accordance with federal law, including the Federal Privacy Act, 5 U.S.C. 562a, and its implementing regulations. DD Form 2005, Privacy Act Statement-Health Care Records, contains the Privacy Act Statement for the records. Records may also be examined by the U.S. Food and Drug Administration.

The Department of Defense will provide medical care for DoD eligible members (active duty, dependents, and retired military) for physical injury or illness resulting from participation in this research. Such care may not be available to other research participants, except in the event of an emergency. Compensation may be available through judicial avenues to non-active duty research participants if they are injured. I understand that my entitlements to medical and dental care and/or compensation in the event of injury are governed by federal laws and regulations, and if I desire further information, I may contact Capt. G. Ralph Moseley or Dr. John P. McDonough.

In the event that an unanticipated event (clinical or medical misadventure) occurs during my participation in this study, I will be informed. If I am not competent at that time to understand the nature of the event, such information will be brought to the attention of my guardian or next of kin.
The decision to participate in this study is completely voluntary on my part. No one has coerced or intimidated me into participating in this program. I am participating because I want to. Capt. Moseley and/or Dr. McDonough have adequately any and all questions I have about this study, my participation, and the procedures involved. I understand that Capt. Moseley and/or Dr. McDonough will be available to answer any questions concerning procedures throughout this study. I understand that if significant new findings develop during the course of this study which may relate to my decision to continue participation, I will be informed. I further understand that I may withdraw this consent at any time and discontinue further participation in this study without prejudice to my entitlements to care. I also understand that the investigator for this study may terminate my participation in this study if he feels this to be in my best interest.

Answers to Questions

If at any time you feel that you may have sustained a research-related injury, you may call Capt. G. Ralph Moseley, SRNA, NC at (301) 589-2971 day or night. You may also call Dr. John P. McDonough, CRNA, Ed.D. at (301) 295-6565 (day) or (301) 315-2338 (night). They will that you receive appropriate medical treatment. If at any time before, during, or after the study you have any questions about the study you may call Capt. Moseley and/or Dr. McDonough at one of the above numbers. If you have any questions about your rights as a research subject, you may call USUHS Director, Research Programs (301) 295-3303 or USUHS General Counsel at (301) 295-3028.

I have fully explained this research, including the risks and alternate treatments, to the subject _____. In my judgment, there was sufficient access to information, including risks and benefits, to make an informed decision to participate in this study.
Investigator's Signature: _____   Date: _____

Investigator's Name (Print): _____

I have read the above description of the research study. I have talked it over with the anesthesia provider, have been given the opportunity to ask questions, and have had those questions answered to my satisfaction. I have also been given a copy of this consent form.

I understand that my participation is entirely voluntary and that I may withdraw my consent at any time, without penalty. I know enough about the purpose, procedures, risks, and benefits of the research study to decide that I want to take part in it.
For Women Able to Bear Children: I understand that if I am pregnant or breast-feeding I may not take part in this study. I am not breast-feeding and to the best of my knowledge, I am not pregnant.

I willingly give my consent to take part in this study.

_____   _____
Patient's Signature   Date and Time

_____
Patient's Social Security Number

_____   _____
Witness' Signature   Date and Time

APPENDIX D

SCRIPT

I.   Initial Interview.

Hello, you have been chosen as a potential candidate for a study involving 2 drugs which are commonly used for the types of surgery you are about to undergo. The two drugs are fentanyl and remifentanil. Both are narcotics and they are useful in treating the pain you might experience during your surgery. Fentanyl has been used since the '60's, but the other drug, remifentanil, has only just recently been approved by the FDA for use in surgery. Since remifentanil is a newer drug, there are still some things that we would like to understand better about it. I am interested in knowing how remifentanil compares to fentanyl with regards to psychomotor recovery after a general anesthetic. Psychomotor recovery refers to things like eye-hand coordination.

Whether or not you choose to participate in this study is entirely up to you. Your decision to participate or to not participate will not in any way effect the quality of care you receive. Your safety will at all times be our number one objective. You may at any time and for any reason decide to quit the study. Are you interested in possibly joining this study? If so, I'll continue…

Again, this is a study between 2 narcotics, fentanyl and remifentanil, which are commonly used in general anesthesia for the type of surgery you're about to undergo. As I said earlier, I'm interested in how quickly you recover your eye-hand coordination postoperatively. To test your eye-hand coordination, I'll be giving you a sort of connect-the-dots game. [Show TD test.] You'll complete this test twice now while you are awaiting your surgery. After your surgery, we'll wait until you're awake and stable enough, then the recovery room nurse will give you the test again. Your recovery room nurse will give you the test four more times, once every thirty minutes. So, you'll complete the test twice now and then five times after your surgery.

Even though you will be a member of this study the first priority will at all times be your safety and making sure that you receive good care before, during, and after your surgery. At no time will your safety be jeopardized for the sake of this study. Again, you may at any time and for any reason decide to quit this study. Your participation in this study is entirely voluntary. Would you like to join this study?…

This is the consent for your agreeing to join the study. Read it carefully before you sign it. There's no tricks, it's merely a longer explanation of what I already told you. Sign only when you feel like you understand it. If you experience any difficulties that you feel may be due your anesthesia, you may contact either myself or Dr. McDonough. Information on how to contact us is in the consent. I will provide you with a copy of it.

Okay, now for your first connect-the-dots test.

II. Trieger Dot Test Instructions.

Connect the dots. You will be given 30 seconds.

APPENDIX E

DATA COLLECTION FORM

Data Collection Form for
PSYCHOMOTOR FUNCTIONING: COMPARISON OF PATIENTS RECOVERING FROM GENERAL ANESTHETIA WITH REMIFENTANIL & AVOLATILE ANESTHETIC VERSUS AFENTANYL & VOLATILE ANESTHETIC

SITE:_____   **MEDICAL RECORDS NUMBER**_____

1. SUBJECT NUMBER:_____   **2. PROCEDURE:**_____

3. AGE:_____   **4. WEIGHT:**_____

5. SEX (circle one): M / F

6. ENGLISH SPEAKING (circle one): Y / N

7. DENIES CURRENT PSYCHIATRIC DISORDER (circle one): Y / N

8. ONGOING PSYCHIATRIC CONSULTS IN PATIENT RECORD (circle one): Y / N

9. USE OF DRUGS THAT MIGHT ALTER MENTATION (*e.g.,* psychotrophic drugs, anxiolytic drugs) (circle one): Y / N

10. ORIENTED TO PERSON, PLACE, TIME, AND REASON FOR ADMISSION PREOPERATIVELY (circle one): Y / N

11. CONSENT FOR INCLUSION IN THE STUDY SIGNED (circle one): Y / N

12. TIME WHEN SUBJECT INDUCED:___:___.

13. TIME OF DC FOR ISOFLURANE: ___:___.

14. AVERAGE AMOUNT OF ISOFLURANE (Et) FOR MAINTENANCE:_____.

15. TOTAL AMOUNT OF FENTANYL (mcg/Kg):_____.

16. TIME OF LAST FENTANYL DOSE:___:___.

17. TOTAL AMOUNT OF REMIFENTANIL (mcg/Kg):_____.

18. LENGTH OF ANESTHETIC TIME (#13 - #12):_____minutes.

19. TIME WHEN SUBJECT SCORED 8 ON ALDRETE SCALE: ___:___ . (This is T_0.)

20. PREOPERATIVE TRIEGER DOT SCORE:_____

21. TRIEGER DOT SCORE UPON ATTAINMENT OF STAGE II OF RECOVERY (T_0):_____

22. T_{30}_____   19. T_{60}_____   20. T_{90}_____   21. T_{120}_____
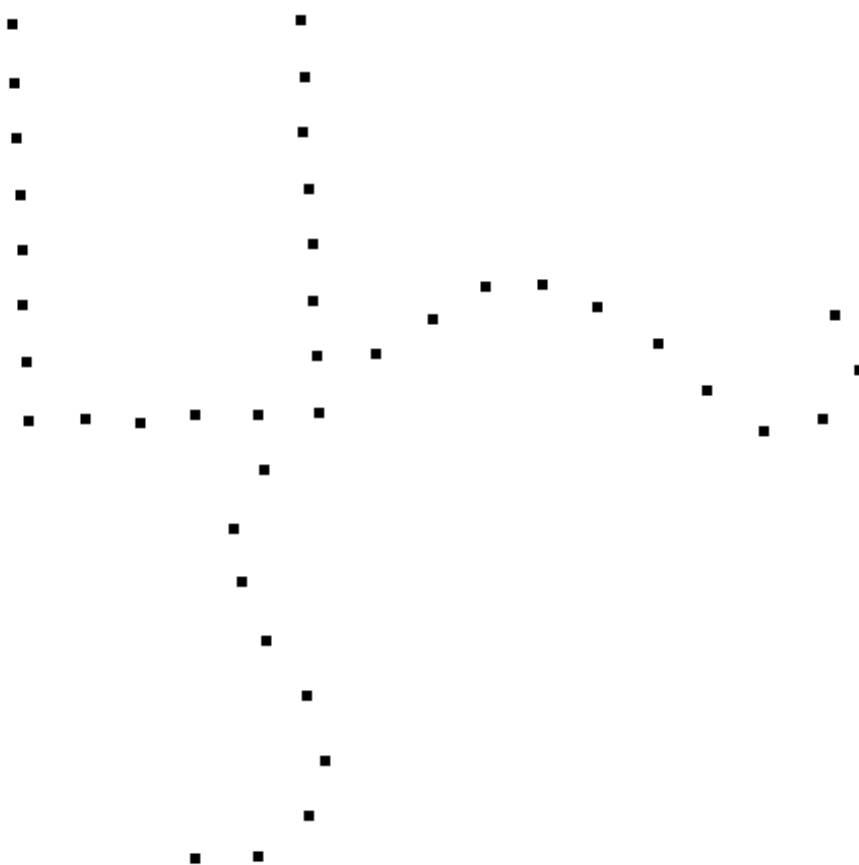
APPENDIX F

TREIGER DOT TEST

SUBJECT NUMBER:___
TIME OF TEST:__:__
NUMBER OF DOTS MISSED:___
POSITION IF OTHER THAN SUPINE:_____

APPENDIX G1

REMIFENTANIL GROUP, ANESTHETIC PROTOCOL

Note: All patients in both arms will receive full peri-anesthetic monitoring and be denitrogenated with 100% oxygen prior to induction of general anesthesia.

1. Administer midazolam 0.5-2mg IV prior to induction.

2. Administer lidocaine 1 mg/kg prior to induction.

3. Administer propofol 1-2 mg/kg for induction.

4. Concurrently with induction agent, begin remifentanil infusion at 0.5 mcg/kg/min.

Note: For obese patients exceeding ideal body weight by $\geq 30\%$, dose at ideal weight.

5. Administer neuromuscular blocking agent per usual practice of supervising practitioner.

6. Perform endotracheal intubation.

7. Decrease remifentanil infusion rate to 0.25 mcg/kg/min. after intubation.

8. Begin nitrous oxide at 66% in oxygen and isoflurane to an end-tidal concentration of 0.4%.

9. Signs of light anesthesia will be treated by increasing remifentanil infusion to a maximum of 1.0 mcg/kg/min.

10. Isoflurane may also be increased in response to hemodynamics not controlled by remifentanil.

11. Postoperative analgesia
    based on projected patient requirements, 20 min. prior to end of surgery IV dose of either:
    morphine 0.1 mg/kg, or
    fentanyl 1 mcg/kg, or
    ketorulac 30 mg

12. Discontinue remifentanil at end of surgery (last stitch or last surgical manipulation).

13. Ondansetron 4 mg IV may be used for prevention of PONV if desired by the supervising practitioner.

APPENDIX G2

FENTANYL GROUP, ANESTHETIC PROTOCOL

Note: All patients in both arms will receive full peri-anesthetic monitoring and be denitrogenated with 100% oxygen prior to induction of general anesthesia.

1. Administer midazolam 0.5-2mg IV prior to induction.

2. Administer lidocaine 1 mg/kg prior to induction.

3. Administer fentanyl 2-3 mcg/kg 2-5 min. prior to induction.

4. Administer propofol 1-2 mg/kg for induction.

5. Administer neuromuscular blocking agent per usual practice of supervising

practitioner.

6. Perform endotracheal intubation.

7. Begin nitrous oxide at 66% in oxygen and isoflurane to an end-tidal concentration of 0.4%.

8. Signs of light anesthesia will be treated by additional doses of fentanyl or increasing isoflurane concentration as per the usual practice of the supervising practitioner.

9. Postoperative analgesia
   based on projected patient requirements, 20 min. prior to end of surgery IV dose of either:
   morphine 0.1 mg/kg, or
   fentanyl 1 mcg/kg, or
   ketorulac 30 mg

10. Discontinuation of the isoflurane will be per the usual practice of the supervising practitioner.

11. Ondansetron 4 mg IV may be used for prevention of PONV if desired by the supervising practitioner.

APPENDIX H

MALCOLM GROW MEDICAL CENTER
IRB APPROVAL LETTER

DEPARTMENT OF THE AIR FORCE
HEADQUARTERS 89TH AIRLIFT WING (AMC)

88 Dec 97

TO: CAPT O RALPH MOSELEY
11420 ROCKVILLE PIKE, SUITE 400B
ROCKVILLE, MD 20852

FROM: 89th MDG/SGI
1050 W PERIMETER RD
ANDREWS AFB, MD 20762-6600

SUBJECT: Approval of protocol "PSYCHOMOTOR FUNCTIONING: COMPARISON
OF PATIENTS RECOVERING FROM GENERAL ANESTHESIA WITH
REMIFENTANIL AND A VOLATILE ANESTHETIC VERSUS A FENTANYL
AND A VOLATILE ANESTHETIC"

The changes that the Institutional Review Board (IRB) recommended to you in reference to the
above mentioned protocol have been received and reviewed. You may begin your study. Please
ensure that all appropriate paperwork be forwarded to our office promptly (i.e., progress, final
reports)

JANICE LEE, Col, USAF, MC
Director, Career Development Function

APPENDIX I

USUHS IRB CORRESPONDENCE

UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES
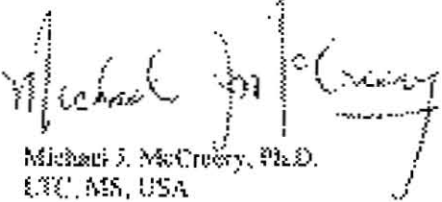4301 JONES BRIDGE ROAD
BETHESDA, MARYLAND 20814-4799

February 10, 1998

MEMORANDUM FOR G. RALPH MOSELEY, DEPARTMENT OF GRADUATE SCHOOL
OF NURSING

SUBJECT: IRB Approval of Protocol T061494H for Human Subject Research

Your research protocol entitled *Psychomotor Functioning: Comparison of Patients Recovering from General Anesthesia with Remifentanil and a Volatile Anesthetic Versus a Fentanyl and a Volatile Anesthetic*, was given full review by the USUHS Institutional Review Board (IRB) on 12/11/97. The protocol will be approved for execution pending revisions to the consent form stipulated by the IRB.

The minutes of the meeting are attached for your convenience. Please submit the revised Informed Consent Document to the Office of Research for review. It is anticipated that approval will be given, provided the stipulations of the IRB are incorporated. If you have any questions regarding the memorandum or human subject research, please do not hesitate to call me at 301-295-3303.

Michael J. McCreery, Ph.D.
LTC, MS, USA
Director, Research Programs and
Executive Secretary, IRB

cc: Director, Grants Administration

Printed on Recycled Paper

INSTITUTIONAL REVIEW BOARD MINUTES
December 11, 1997

E. T08077-01 *Psychomotor Functioning: Comparison of Patients Recovering from General Anesthesia with Remifentanil and a Volatile Anesthetic vs. Fentanyl and a Volatile Anesthetic* by Captain G. Ralph Moseley, SRNA, and John P. McDonough, CRNA, Ed.D., is a study using a cohort of thirty individuals. The hypothesis is that the 15 subjects to whom Remifentanil will be administered will regain psychomotor function more quickly than those under the influence of Fentanyl. The patients will be asked to perform a "connect-the-dots" test both before and after surgery. The pre-operative test will establish a baseline for each subject's performance. This will be compared with the subject's post-operative performance of the same test. Although the age and condition of the subject will vary, as will the type of surgery, it is hoped that the size of the sample will make up for these variables.

The Committee had several comments. If the ICD is going to state that the subject is going to be administered one of two drugs, then it should state not only the names of the drugs but describe their effects. Since the choice of the drug will be left up to the anesthetist or anesthesiologist, what is unique about the study is the "connect-the-dots" test. Since the subjects have already consented to surgery and to anesthesia, all that this ICD need provide for is consent to the test.

ACTION   Motion   Approve protocol subject to modification of consent as suggested above.

REPLY TO   23 March 1998
 ATTN OF: G. Ralph Moseley, Capt, USAF, SRNA

SUBJECT: ICD Modifications

TO: USUHS IRB

1. Attached is the modified ICD for the research protocol entitled *Psychomotor Functioning: Comparison of Patient's Recovering from General Anesthesia with Remifentanil and a Volatile Anesthetic Versus Fentanyl and a Volatile Anesthetic*.

2. The modifications were based on the IRB Minutes from the 11 December, 1997 meeting.

3. If there are any questions regarding this matter, my home phone number is 301-589-2971. Please leave a message on my answering machine if I am not home.

G. RALPH MOSELEY, Capt, USAF, SRNA   1 Atch
Principal Investigator   REVISED ICD

cc: Thesis Committee Chair

APPENDIX J

USUHS IRB APPROVAL LETTER

UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES
4301 JONES BRIDGE ROAD
BETHESDA, MARYLAND 20814-4799

March 24, 1998

MEMORANDUM FOR CAPTAIN G. RALPH MOSELEY, USAF, SRNA, GRADUATE
SCHOOL OF NURSING

SUBJECT: IRB Approval of Protocol T06349-01 for Human Subject Research

Your research protocol entitled *Psychomotor Functioning: Comparison of Patients Recovering from General Anesthesia with Remifentanil and a Volatile Anesthetic Versus a Fentanyl and a Volatile Anesthetic*, was given full review by the USUHS Institutional Review Board (IRB) on 12/11/97 and was approved for execution pending revisions to the consent form stipulated by the IRB. These revisions have been received and have been reviewed and approved.

The consent form approved for use is attached. Please use photocopies of the stamped and approved informed consent document when obtaining consent from subjects being enrolled. It is your responsibility to maintain an accurate and accessible file of all consent forms of participating human subjects. An on-site review of this project with regard to human subject use will be scheduled one year from the project approval date.

Please notify this office of any amendments you wish to propose and of any adverse events which may occur in the conduct of this project. If you have any questions regarding human subject research, please do not hesitate to call me at 301-295-3303.

Michael J. McCreery, Ph.D.
LTC, MS, USA
Director, Research Programs and
Executive Secretary, IRB

cc: Director, Grants Administration